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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/795,933	03/08/2004	Jan Zavada	D-0021.2-2	2689

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
11/15/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/795,933	ZAVADA ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-35 and 39-55* is/are pending in the application.

4a) Of the above claim(s) *41-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-35,39,40 and 53-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on and September 12, 2007.

Currently, claims 31-35, 39-40, and 53-55 are under examination on the merits in the instant case.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112

Claims 31-35, 39-40, and 53-55 remain rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement for the reasons of record as set forth in the Office action mailed on June 12, 2007 and for the reasons stated below.

Applicant's arguments filed on September 12, 2007 have been fully considered but they are not persuasive. Applicant argues that the claimed invention because there is no objective

evidence as to why the instantly claimed methods would not work. Contrary to applicant's argument, the seven factors that determine the enablement requirement under 35 U.S.C. 112, first paragraph were objectively assessed as stated in the Office action mailed on June 12, 2007. See pages 4-7. To reiterate, the breadth of the claims (see factor A) embraces DNA vector comprising 19 to 29-mer antisense oligonucleotide that is transcribable in cells usable in pharmaceutical applications, wherein the vector is a plasmid, a cosmid, a bacteriophage, or a virus, and a method of inhibiting the target gene *in vivo* in a human comprising administering the DNA vector in therapeutic applications. The nature of the invention (see factor B) is pharmaceutical or therapeutic, and more precisely, it pertains to gene therapy. The state of the prior art (see factor C), which means prior to the earliest priority date of October 21, 1992, was nascent and far from being well-established to the extent that no adequate working example commensurate in scope with the claimed invention was necessary. This fact is further substantiated by applicant's prior art references, none of which taught *in vivo* experimental, objective data comprising administering a bacteriophage vector, for example, comprising an antisense oligonucleotide to treat a neoplastic disease in a human. Further, none of the applicant's cited references teaches that the claimed "expression control sequence" derived from the "MN promoter" is operable in expressing a short antisense oligonucleotide in cells. As such, the complete lack of prior art teachings commensurate in scope with the claimed therapeutic methods or claimed MN antisense construct corroborates the objective fact that the antisense oligonucleotide-mediated gene therapy prior to the year of 1992 was not as advanced as the current state of the art. The level of one of ordinary skill (see factor D) and the level of predictability in the art (see factor E) are contingent upon the state of the prior art. Hence, the

skills, techniques, and knowledge required to make and use the claimed invention commensurate in scope with the claims were insufficient and therefore making and using the claimed invention were unpredictable at the time the invention was made in 1992. The amount of direction provided by the inventor (see factor F) is not sufficient because the specification as originally filed does not provide any practical information as to how to construct the claimed antisense oligonucleotide (19-29 mer) vector or how to treat a human with a neoplastic disease by administering such vector. The existence of working examples (see factor G) is nadir because no relevant working examples as to how to make the claimed antisense oligonucleotide vector or how to practice the claimed therapeutic method *in vivo* are present in the specification as filed. The only example pertinent to "antisense" is an *in vitro* example wherein naked antisense oligonucleotides, not vectors comprising antisense oligonucleotides transcribable are transfected into tumor cells. That is, the specification fails to adequately describe the claimed invention as to enable any person skilled in the pertinent art to make and use the claimed invention at the time of the invention as required by 35 U.S.C. §112, first paragraph. With regard to disclosing working examples, MPEP 2164.02 teaches that "Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art." Note that "if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling." See MPEP 2164.03.

See also *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) which teaches the following: "Nascent technology, however, must be enabled with a ***"specific and useful teaching"***. The law requires an enabling disclosure for nascent

technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (original emphasis)

The quantity of experimentation need to make or use the invention based on the content of the disclosure (see factor H) would have been undue at the time of the invention because no adequate direction and working examples that are commensurate in scope with the claimed invention are provided in the content of the disclosure, nor were the state of the prior art, the level of one of ordinary skill in the art, and the level of predictability in the art were such that no direction or guidance from the inventor was necessary to make and use the claimed invention as of October 21, 1992.

Applicant cites *In re Marzochhi* and *In re Brana*, to allege that there is no reason to doubt the objective truth of the statements relied upon for enabling support in the specification for the claimed invention. Contrary to applicant's allegation, the disclosure of the specification was nowhere close to "enabling" for the reasons stated above. Furthermore, applicant's citation of the case laws further demonstrates that the instant specification was far from being "enabling", because the specification disclosure of the instant application does not contain "a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject mater sought to be patented". Since the instant specification as filed is silent about the manner and process of making and using the claimed vector and methods comprising antisense oligonucleotides corresponding in scope to the vector and methods sought to be patented, the case laws cited by applicant are irrelevant to the issues in the instant case.

Applicant asserts that "at the time of filing an application, an applicant needs not have any examples" if there is "objective enablement" by citing *In re Vaeck*. Since there is no objective enablement in the instant specification, applicant's assertion is irrelevant in the instant case. Further, the court expressly stated in *In re Vaeck*, "Specification ***must***, in order to be enabling as required by 35 USC 112, first paragraph, teach person skilled in the art to make and use invention without "undue experimentation," which does not preclude some experimentation" (emphasis added). The court further expressed at 1445, "However, there ***must*** be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed...In this case, we agree with the PTO that appellants' limited disclosure does not enable one of ordinary skill to make and use the invention as now recited in claims 1-46 and 50-51 without undue experimentation." In other words, the court ruled that a rejection under 35 U.S.C. 112, first paragraph for lack of enablement was appropriate given the relatively incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims.

Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of treating a human comprising administering a vector containing an antisense oligonucleotide. For an actual reduction to practice, the invention must have been sufficiently tested to demonstrate that it will work for its intended purpose, but it need not be in a commercially satisfactory stage of development. See *Scott v. Finney*, 34 F.3d 1058, 1062, 32 USPQ2d 1115, 1118-19 (Fed. Cir. 1994). (emphasis added)

See also *In Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 52 USPQ2d 1129

(Fed. Cir. 1999), in which the court held that claims in two patents directed to genetic antisense technology (which aims to control gene expression in a particular organism), were invalid because the breadth of enablement was not commensurate in scope with the claims. Both specifications disclosed applying antisense technology in regulating three genes in E. coli. Despite the limited disclosures, the specifications asserted that the "[t]he practices of this invention are generally applicable with respect to any organism containing genetic material which is capable of being expressed ... such as bacteria, yeast, and other cellular organisms." The claims of the patents encompassed application of antisense methodology in a broad range of organisms. Ultimately, the court relied on the fact that (1) the amount of direction presented and the number of working examples provided in the specification were very narrow compared to the wide breadth of the claims at issue, (2) antisense gene technology was highly unpredictable, and (3) the amount of experimentation required to adapt the practice of creating antisense DNA from E. coli to other types of cells was quite high, especially in light of the record, which included notable examples of the inventor's own failures to control the expression of other genes in E. coli and other types of cells. Thus, the teachings set forth in the specification provided no more than a "plan" or "invitation" for those of skill in the art to experiment using the technology in other types of cells.

Applicant further relies on the declaration under 37 CFR 1.132 filed on January 4, 2007, which is insufficient to overcome the rejection of claims 31-35, 39-40, and 53-55 based upon insufficiency of enabling disclosure under 35 U.S.C. 112, first paragraph, as set forth in the last Office action for the following reasons:

First and foremost, the declaration is directed to the inventions claimed in Application No. 08/260,190, now a U.S. Patent 6,774,117 B1. The claimed subject matter in 08/260,190 are directed to method of treating neoplastic disease *in vivo* comprising administering a naked antisense oligonucleotide in a physiologically acceptable carrier. As such, the claimed subject matter in the instant case essentially differ from that in 08/260,190, to which the declaration filed on January 4, 2007 is directed.

Second, the declarant states that the *in vitro* results comprising naked antisense oligonucleotides shown in the specification correlates with *in vivo* therapeutic efficacy. Again, the subject matter addressed and declared by the declarant is not the subject matter claimed in the instant case.

Third, the declarant declarant that the plasmid containing an antisense MN cDNA has an opposite effect compared to sense nucleic acids, and therefore the MN expression is strongly correlated with tumorigenesis. Again, the claimed subject matter in the instant case is not directed to the lengthy cDNA that is in antisense orientation. Rather, it is directed to vector (plasmid, cosmid, bacteriophage, virus) containing a short antisense oligonucleotide transcribable in cells. Further, whether or not the target gene expression is correlated with tumorigenesis is irrelevant in the instant case, because no adequate disclosure of target gene inhibition by the claimed vector comprising a short antisense oligonucleotide is shown in the specification.

Lastly, there is nothing on the record in the declaration that suggests or indicates that the presently claimed invention was fully enabled in the art. The declaration is entirely devoted to asserting that the antisense ODNs claimed in 08/260,190 would have worked in treating diseases

in vivo without undue experimentation. Since there is no nexus between the subject matter claimed in the instant case and that described by the declarant, the declaration bears no substantive, objective evidence that the claimed invention in the instant case was fully enabled.

In light of the totality of the evidence, factors, and reasons considered in the instant case, this rejection is maintained.

Conclusion

No claim is allowed.

This application contains claims 41-52 drawn to inventions nonelected withour traverse in the reply filed on March 16, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
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Art Unit 1635

/J. E. Angell/
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